REMARKS

Upon entry of the Amendment, claims 1-29, 31-34, 38, 44-46 and 48-51 are pending in the application. Claims 1-26, 33, 34, 38, 44, 46, and 48-51 are withdrawn. Claims 27-32 and 45 are under consideration. Claim 27 has been amended. Claim 30 is canceled. Support for the amendment to claim 27 reciting "fresh cells" can be found in the specification, such as in Example 8. The subject matter of canceled claim 30 has been incorporated into claim 27. Therefore, no new matter has been added.

Further, Applicants respectfully request rejoinder of claim 48. Claim 48 depends from claim 27, which is under consideration.

I. Claim Rejections - 35 U.S.C. § 112

Claims 27-32 and 45 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Referring to pages 3 to 7 of the Office Action, the Examiner asserts that a person skilled in the art cannot use the claimed method to diagnose a bipolar disorder in a patient without undue experimentation. The Examiner asserts that the claimed method contradicts the teachings in the specification. The specification describes that one would not expect transmembrane potential to serve as a reliable basis for diagnosing bipolar disorder in an individual patient, because measurements of transmembrane potential are highly variable. *See* page 7, lines 7-11. Further, the Examiner asserts the results in El-Mallakh, *et al.* "Leukocyte transmembrane potential in bipolar illness," J. Affect. Disord. 41:33-37 (1996) ("El-Mallakh") contradict the results in Buss *et al.* "Lymphoblastoid transmembrane potential in bipolar patients, their siblings, and unrelated healthy comparison subjects," Psychiatry Research 59:197-201 (1996) ("Buss").

Buss discloses that the "preliminary" data thereof "suggests" that transmembrane potential is a state rather than a trait-related matter. *See* page 197. In contrast, El-Mallakh discloses that pathologic moods in bipolar illness may be associated with altered cellular membrane physiology. *See* page 33.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants are not required to explain why the claimed invention is able to diagnose bipolar disorder in a patient. An inventor does not need to disclose why the invention works in order to obtain a patent. *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989). Section 112 states that the specification must describe how to make and use the invention. In this regard, Applicants need not explain why the claimed method is able to diagnose bipolar disorder in a patient. If Applicants need not explain "why" the claimed invention works, Applicants of course need not further explain the reasons why the art previous to the claimed invention provided contradictory results.

The specification provides evidence that the claimed method reliably diagnoses bipolar disorder in patients. Example 4 provides a detailed description of using the method as recited in claim 27, using the elected species of ethacrynate. Examples 5-7 provide a detailed description of using the method as recited in claims 27, using the non-elected species. The results from the experiments demonstrate that the claimed method produces a statistically significant, reliable result in the diagnosis of bipolar disorder.

Moreover, the experiments described in Examples 8-10 provide the results of further, real world applications of the claimed method, again demonstrating that the claimed method produces a statistically significant, reliable result in the diagnosis of bipolar disorder. Examples 8-10 confirms that the results of the trials are consistent with the prior diagnosis of the patients.

Applicants have provided a detailed description of the invention, the manner in which the invention can be used, and the results from numerous experiments demonstrating that the claimed method can be used in a statistically significant, reliable manner. While El-Mallakh and Buss might have suggested that a method of bipolar disorder diagnosis based on sodium pump activity could not be conducted in a reliable manner, Applicants have overcome the obstacles noted in the art and have clearly established that such a method of diagnosis can serve as a reliable basis for diagnosing bipolar disorder in the specification. The Examples disclosed in the specification are evidence that membrane potential is a reliable basis for diagnosing bipolar disorder in a patient.

In any event, in an effort to advance the prosecution, Applicants note that there are technical reasons explaining why the results in El-Mallakh and Buss provide different results. El-Mallakh discloses using mononuclear leukocytes isolated from fresh blood, during normal phase or manic and hypomaniac episodes. *See* page 34, left column. In contrast, Buss discloses using cultured lymphocytes purchased from the National Institute of General Medical Science Human Mutant Cell Repository (Coriell Institute for Medical Research). *See* page 198, right column. The Coriell Institute prepares the cultured lymphocyte thereof by immortalizing lymphocytes from blood with a virus. *See*, http://ccr.coriell.org/Sections/Support/Global/Lymphoblastoid.aspx?PgId=213#1 (last visited July 27, 2007). Buss itself acknowledges that cultured lymphoblastoid cells may not accurately reflect in vivo physiology. *See* page 200, right column. In this regard, a person skilled in the art would appreciate that the differences between El-Mallakh and Buss are based on technical reasons, rather than to conclude all transmembrane potential measurements are not useful for diagnosing bipolar disorder in a patient.

Further, the specification discloses "one would not expect transmembrane potential to serve as a reliable basis for diagnosing a bipolar disorder in an individual patient, because measurements of transmembrane potential are highly variable." *See* page 7 of the specification. However, this statement was provided to describe the background of the invention, rather than the claimed invention itself.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this portion of the rejection.

II. Claim Rejections - 35 U.S.C. § 103

Claims 27-32 and 45 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over El-Mallakh in light of Garrahan *et al.* "The Behavior of the Sodium Pump in Red Cells in the Absence of External Potassium," *J. Physiol.* 192: 159-174 (1967) ("Garrahan") or Antia *et al.* "The upregulation of Na+, K+ -ATPase pump numbers in lymphocytes from the first degree unaffected relatives of patients with manic depressive psychosis in response to in vitro lithium and sodium ethacrynate," *Journal of Affective Disorders*, 34: 33-39 (1995) ("Antia").

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

El-Mallakh discloses as follows:

> [a]fter obtaining baseline TMP measurement 10μl of 2mM gramicidin (Sigma), a depolarizing agent [i.e., gramicidin] dissolved in DMSO, was added and fluorescence recorded. Relative TMP were expressed as a ratio of fluorescence intensity at baseline over fluorescence of gramicidin-treated (depolarized) cells as modified from Kessel et al. (1991).

See page 34, left column, line 45, to right column, line 7.

El-Mallakh fails to disclose comparing its relative TMP to another sample. El-Mallakh discloses the demographic data of its normal control, euthymic bipolar, and manic/hypomanic

subjects. *See* page 35, Table 2. However, this disclosure explains the demographic of human subjects from whom the researchers thereof extracted the cells. It does not compare the actual relative TMP of its subjects. El-Mallakh discloses that the human subjects were recruits who had already been diagnosed as being normal, euthymic bipolar, and manic/hypomanic. *See* page 34, left column.

As such, El-Mallakh fails to disclose or suggest comparing the patient ratio to a control ratio and/or bipolar control ratio. While El-Mallakh discloses the demographics of its pool, El-Mallakh fails to disclose comparing the relative TMPs thereof for the purpose of diagnosing a bipolar disorder. The researchers of El-Mallakh already knew whether the patients thereof were or were not afflicted with euthymic bipolar or manic/hypomanic disorders. El-Mallakh is deficient in that it fails to teach or suggest comparing the patient ratio to a control ratio and/or bipolar control ratio.

Both Garahhan and Antia fail to alleviate this deficiency in El-Mallakh. Garrahan is relied upon for teaching various different conditions including the presence or absence of potassium ion. Antia is relied upon for teaching ethacrynate. These teachings having nothing to do with comparing the patient ratio to a control ratio and/or bipolar ratio.

Further, the method presently recited in claim 27 provides for unexpectedly superior results. The Declaration by Dr. Thiruvengadam provides evidence. Examples 3 and 4 of the specification demonstrate that samples of unaffected and affected cells provide for differences in membrane potential where cells incubated *in vitro* in the presence of the compound that alters Na^+K^+ ATPase activity are incubated *in vitro* in the absence of K^+, and wherein the cells incubated *in vitro* in the absence of the compound that alters Na^+K^+ ATPase activity are incubated *in vitro* in the presence of K^+. In contrast, the Declaration shows that bipolar cells and

negative cells do not provide for a significant difference where the cells are incubated in K^+ in each incubation. As a result, the Declaration provides evidence that the method presently recited in claim 27 provides for unexpectedly superior effects.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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